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Increase in atopic sensitization rate among Dutch children with symptoms of allergic disease between 1994 and 2014

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Abstract

Background: The prevalence of symptoms of allergic diseases has increased significantly during the last decades. However, studies into time trends of atopic sensitization among children are limited and have focused on aeroallergen sensitization. We aimed to investigate time trends in the prevalence and degree of atopic sensitization to inhalant and food allergens among children (0-17 years) with symptoms of allergic disease.

Methods: Sensitization data of all children tested in our clinical laboratory during 1994-2014 were analyzed. Sensitization was detected using the ImmunoCAP system and defined as a specific IgE level of ≥0.35 kU/L. Trends in sensitization rates to 5 food and 5 aeroallergens for different age categories were investigated with logistic regression, adjusted for age and sex.

Results: Sensitization data of 18 199 children were analyzed. Between 1994 and 2014, a steady and statistically significant increase in overall sensitization rate was found (from 40.5% in 1994 to 48.9% in 2014, adjusted odds ratio [aOR] 1.01 per year, 95% confidence interval [CI] 1.00 to 1.01, $P = .003$). This increase in sensitization rate was mainly explained by increasing aeroallergen sensitization among 4- to 11-year-old children (aOR 1.02, 95% CI 1.01 to 1.02, $P < .001$). We found no increase in sensitization rates to food and aeroallergens in other age categories. The degree of sensitization did not change significantly during the study period (all tests $P > .15$).

Conclusion: We observed a statistically significant increase in sensitization rate between 1994 and 2014 among children with symptoms of allergic disease. This was mainly explained by increasing aeroallergen sensitization among 4- to 11-year-olds.

KEYWORDS

aeroallergen, atopic sensitization, children, epidemiology, food allergen

1 | INTRODUCTION

The prevalence of allergic disease has increased significantly in developed countries during the last decades of the 20th century.[1-4] However, most studies into time trends in the prevalence of allergic disease have been questionnaire based, assessing symptoms and doctor's diagnosis of disease. Only a limited number of studies used more objective markers of allergic disease, such as atopic sensitization.[5]

Those few studies exploring changes in the prevalence of atopic sensitization over time in children show conflicting results. The prevalence of skin prick test reactivity or the presence of specific immunoglobulin E (IgE) to common aeroallergens remained stable in general population-based surveys in Switzerland, Denmark, and Australia between 1986 and 2002.[6-8] On the contrary, a Swedish study showed

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IQR, interquartile range.

an almost 50% increase in sensitization rate to aeroallergens in 7- to 8-year-old children between 1996 and 2006.[9]

Most studies performed among children investigated sensitization to aeroallergens. Only 2 studies reported time trends in food allergen sensitization. One found that the prevalence of a positive skin prick test to peanut increased from 1.3% in 1989 to 3.3% in 1994, but had decreased to 2.0% by 2001.[10] A large US study found no change from 1988-1994 to 2005-2006 in the prevalence of sensitization to peanut, hen's egg, and cow's milk.[11]

Although changes in the diagnosis of food allergy over time have been reported,[12] there remains a paucity of studies exploring changes over time in the sensitization to both aeroallergens and food allergens in children, particularly in children with symptoms of allergic disease. The aim of this study was to examine changes in the prevalence and degree of atopic sensitization to aeroallergens and food allergens in children with symptoms of allergic disease in the Netherlands between 1994 and 2014.

2 | METHODS

2.1 | Study design

This was a retrospective study analyzing all specific IgE tests carried out in children (0-17 years) in the clinical laboratory of Isala Hospital, Zwolle, between 1994 and 2014. These children were referred for allergy testing by their primary or secondary care physician because of allergic symptoms. In the Netherlands, specific IgE testing is by far the most commonly used test to examine atopic sensitization in children, both by general practitioners and by pediatricians.

2.2 | Procedure

As described in more detail previously,[13,14] blood samples were investigated with a screening test for aeroallergens, food allergens, or both (Phadiatop, FX5, or Phadiatop infant, Thermo Fisher, Uppsala, Sweden). In case of a positive screening test, specific IgE to an extensive panel of common aeroallergens and food allergens was assessed using the ImmunoCAP system (Thermo Fisher, Uppsala, Sweden). A specific IgE level of 0.35 kU/L or greater was considered to reflect sensitization to the specific allergen. Details on clinical symptoms and diagnosis were not available.

2.3 | Analysis

We analyzed time trends in the prevalence and degree of sensitization to the 5 most common aeroallergens (house dust mite, grass and tree pollen, cat and dog dander) and food allergens (cow's milk, hen's egg, soy, wheat, and peanut), adjusted for age and sex. The degree of sensitization of children was determined by the number of sensitizations found. We classified children as being sensitized to 1, 2 to 4, or 5 or more allergens, respectively, as previously described.[13] Statistical analysis was performed with SPSS 22 (IBM logistics, Chicago, IL, USA). Proportions were compared with chi-squared test, and continuous data with Mann-Whitney *U* test because of nonparametric distributions. To assess time trends in sensitization rate adjusting for age at blood test and sex, an ordinal logistic regression model with backward selection was used. Time trend analysis was also performed in age subgroups: 0- to 3-year-olds, 4- to 11-year-olds, and 12- to 17-year-olds, reflecting preschool, primary and secondary school age groups.

2.4 | Multiple tests

Approximately 10% of the investigated children were tested more than once for atopic sensitization. In those children, we conducted 2 analyses, 1 using the most recent sample and 1 using the first test performed, to avoid potential selection bias of higher sensitization rates in later samples.

2.5 | Ethical considerations

Under Dutch law, a retrospective study anonymously analyzing patient data, as was the case in this study, is exempt from formal medical ethical evaluation. A statement to that effect was issued by the hospital ethical review board.

3 | RESULTS

Between 1994 and 2014, a total of 20 624 blood samples of 18 199 children (51.4% boys) were tested for atopic sensitization. Tested girls were significantly older than boys (median [interquartile range, IQR] 10.1 [5.5 to 14.9] vs 7.6 [4.4 to 12.1] years, respectively, $P < .001$). Not all children were screened for both food and aeroallergen sensitization. This differed per age group (Figure 1).

In children with multiple sensitization tests, results using the last and the first samples yielded comparable results. Therefore, we only present results of analyses using the last sample in these patients. Results of analyses using the first sample showed comparable results (Appendix S1).

A total of 8947 children were screened for both food allergens and aeroallergens. Of those 8947, 7440 children were screened with Phadiatop and FX5. Seven hundred and forty-nine children aged 0-3 years were screened with Phadiatop infant and FX5. Seven hundred and fifty-eight children 0-3 years of age were screened for food allergen and aeroallergen sensitization using only Phadiatop infant.

Overall, 8208 children (45.1% of the study population) were sensitized to 1 or more allergens. The changes seen in sensitization rate during the study period are presented in Figure 2. The prevalence of sensitization increased consistently from 40.7% in 1994 to 48.2% in 2014 (Figure 2). After adjustment for age and sex, this increase was statistically significant (adjusted odds ratio [aOR] for each year after 1994 1.01, 95% CI 1.00 to 1.01, $P = .003$). Aeroallergen sensitization also increased over time (aOR 1.01, 95% CI 1.01 to 1.02, $P < .001$), while food allergen sensitization decreased (aOR 0.97, 95% CI 0.96 to 0.98, $P < .001$). The time trends of atopic sensitization in different

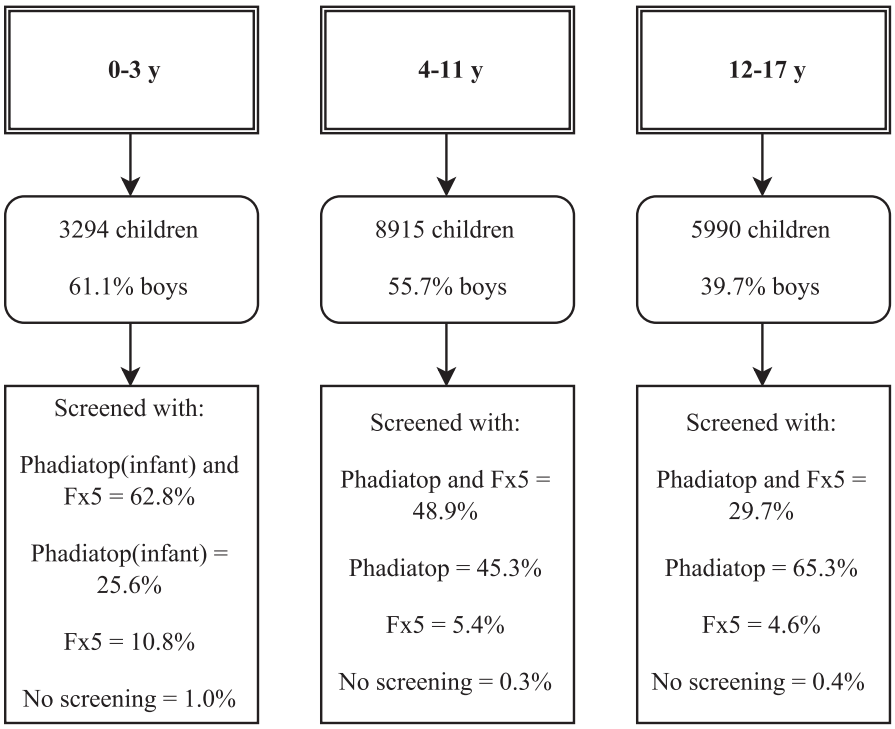

FIGURE 1 Screening methods used for sensitization testing in children in different age groups

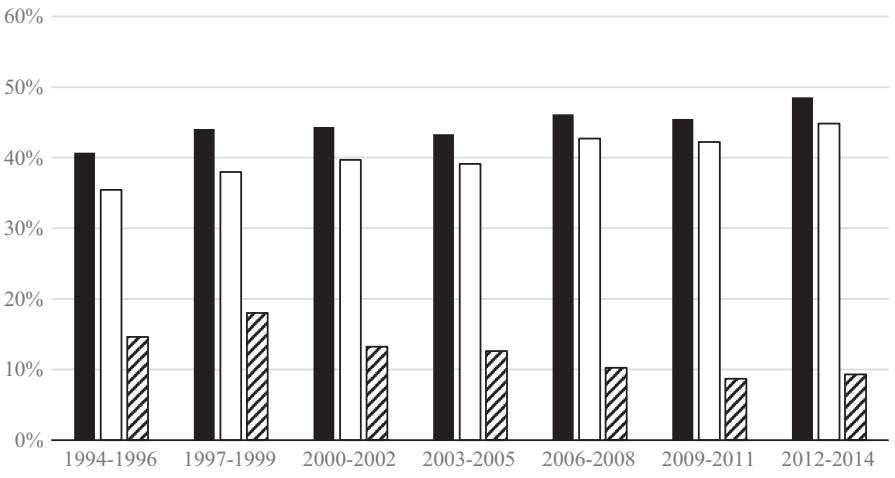

FIGURE 2 Percentage of children with sensitization to 1 or more allergens over time from 1994 to 2014: overall allergic sensitization (black bars), aeroallergen sensitization (white bars), and food allergen sensitization (hatched bars)

age categories are presented in Table 1. The increase in aeroallergen and overall sensitization rates was mainly determined by the changes among children of 4-11 years old.

Changes over time in the degree of atopic sensitization (the number of atopic sensitizations per sensitized child) were analyzed in the 8199 children (45.1% of the total population) who were screened for sensitization to both aeroallergens and food allergens. Of these 8199 children, 3755 (45.8%) were sensitized to 1 or more allergens. Changes over time in the proportion of children sensitized to 1, 2 to 4, and 5 or more inhalant and food allergens are presented in Figure 3. There were no significant changes over time in the proportion of children sensitized to 1, 2 to 4, or 5 or more allergens (all *P*-values > .15). We found no significant time trend either in the severity of aeroallergen sensitization and food allergen sensitization, respectively.

4 | DISCUSSION

This study shows a small but steady and statistically significant increase over time in the proportion of Dutch children sensitized to one or more allergens between 1994 and 2014, while the degree of sensitization in sensitized children remained stable. The increase in sensitization rates over time was largely explained by an increase in aeroallergen sensitization among 4- to 11-year-old children. Between 1994 and 2014, the children tested became almost 20% more likely to be sensitized to one or more (aero)allergens. There were no significant changes over time in other age categories. The prevalence of food allergen sensitization actually decreased over time.

A large and consistent body of evidence shows that the prevalence of symptoms of allergic disease has risen markedly, both among children and adults, in the second half of the 20th century.[15-19] Although

TABLE 1 Time trends in sensitization rate

Age category	Overall sensitization	Aeroallergen sensitization	Food allergen sensitization
0-3 y	1.00 (0.99-1.01) *P* = .94	1.00 (0.99-1.01) *P* = .98	1.00 (0.99-1.02) *P* = .30
4-11 y	1.01 (1.00-1.02) *P* < .001	1.02 (1.01-1.02) *P* < .001	0.94 (0.93-0.95) *P* < .001
12-17 y	1.00 (0.99-1.01) *P* = .66	1.00 (0.99-1.01) *P* = .52	0.96 (0.94-0.98) *P* < .001

Time trends for overall, aeroallergen, and food allergen sensitization. Results are presented as adjusted odds ratios [OR] for each year from 1994 to 2014, 95% confidence interval, and *P*-value.

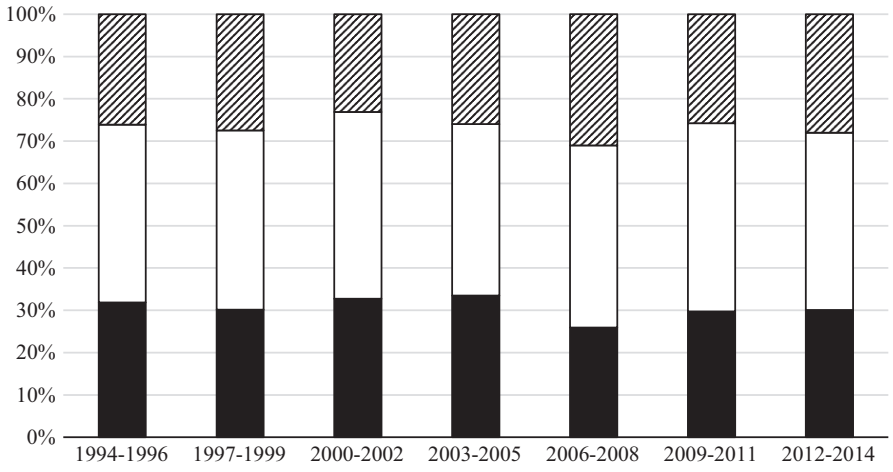

FIGURE 3 Percentage of sensitized children with 1 sensitization (black), 2-4 sensitizations (white), and 5 or more sensitizations (hatched) over time from 1994 to 2014

some studies suggest that the prevalence of allergic diseases continues to rise, several recent studies indicate that this prevalence has plateaued in the Western world.[8,19-22] The large majority of studies examining time trends of prevalence of allergic diseases were questionnaire based. Only a few studied changes in atopic sensitization over time,[6-11,19] and most of these focused on aeroallergen sensitization.[6-9,19] All these studies were based on general population samples, the results of which are not necessarily applicable in clinical practice, in which patients with symptoms of allergic disease are being examined. Our study is the first to investigate changes over time in the prevalence and degree of atopic sensitization among children tested for allergic sensitization by their primary or secondary care physicians, because of symptoms of allergic disease.

Previous studies among adults indicate increasing trends in aeroallergen sensitization over time, even after 1990.[21-23] Results in children, however, have been inconsistent. Only 1 previous study, from Northern Sweden, showed a significant increase in positive skin prick tests to ten common aeroallergens in 7- to 8-year-old children (21% in 1996 and 30% in 2006).[9] Studies from Australia and Germany, however, showed no change in aeroallergen sensitization rates in children between 1992 and 2001-02,[8,19] and a Danish study even showed a decrease in the prevalence of positive skin prick tests to 9 common aeroallergens in children from 24.1% in 1986 to 18.9% in 2001.[21] The present study showed a steady increase in aeroallergen sensitization over time, from 34.5% in 1994 to 45.2% in 2014. Based on the studies performed to date, therefore, no clear time trend in aeroallergen sensitization patterns in children can be distinguished.

Our finding of a decrease in the prevalence of food sensitization among 0- to 17-year-old children between 1994 and 2014 appears to be in concordance with the two previous studies on this issue. In the UK, the prevalence of positive skin prick tests to peanut changed from 1.3% in 1989 to 3.3% in 1994 and to 2.0% in 2001.[10] A large US study showed a nonsignificant decrease in the prevalence of sensitization to egg, milk, peanut, and shrimp from 24.3% in 1988-1994 to 21.6% in 2005-2006.[11]

The reasons for the increase in symptoms of allergic disease in developed countries are only partly understood. It is thought that environmental factors operating in early life play a major role in skewing the immune system toward an allergy-type response.[24-26] Our finding that the increase in sensitization between 1994 and 2014 is limited to aeroallergen sensitization in 4- to 11-year-olds has implications for our understanding of the allergy epidemic in two ways. First, it is compatible with the observation that the increase in allergic disease appears to have plateaued in recent years. If the prevalence of allergic diseases was still increasing, we would have expected an increase in sensitization in 0- to 4-year-olds as well. Second, the predominance of aeroallergen sensitization suggests that exposure to environmental allergens through inhalation may play a role in driving the increase in allergic disease in developed countries, in addition to environmental influences exerting their influence via the gut microbiota.[27,28]

Although the increase in atopic sensitization was consistent and significant in our study population, it was not accompanied by an increase in the degree of atopic sensitization. This is in conflict with the only other study examining this, which was conducted in Northern

Sweden, and showed not only an increase in the prevalence but also in the degree of sensitization.[9]

Because of the divergence in time trends between self-reported or doctor's diagnosis allergic disease and actual atopic sensitization, it has been suggested that the relationship between sensitization and IgE-mediated allergic disease may have changed over time.[11] This complicates the clinical interpretation of sensitization tests, which is already challenging particularly for polysensitized individuals.[13] The results of specific IgE sensitization tests should always be interpreted with the pertinent clinical history and physical examination findings in mind, and not be used as an independent basis for recommendations on allergen avoidance.[29]

The strengths of our study include its large sample size (18 199 blood samples), allowing for robust analysis of time trends in different age groups. All tests were performed in a single laboratory with a standardized protocol. To our knowledge, our study is the first to research time trends of both food and aeroallergen sensitization on this scale.

The main limitation is the lack of clinical details of the patients: Exact symptoms of the children and diagnosis were unknown. This poses the risk of confounding by varying referral of children with different allergic diseases or different severity of disease over time.

In conclusion, the prevalence of atopic sensitization among Dutch children referred for allergy testing with symptoms of allergic disease increased between 1994 and 2014, due to an increase in aeroallergen sensitization in 4- to 11-year-olds. There were no increases in other age groups; food allergen sensitization actually decreased over time.

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REFERENCES

1. Christie GL, Helms PJ, Godden DJ, et al. Asthma, wheezy bronchitis, and atopy across two generations. *Am J Respir Crit Care Med*. 1999;159:125-129.
2. van Schayck CP, Smit HA. The prevalence of asthma in children: a reversing trend. *Eur Respir J*. 2005;26:647-650.
3. Grize L, Gassner M, Wuthrich B, et al. Trends in prevalence of asthma, allergic rhinitis and atopic dermatitis in 5-7-year old Swiss children from 1992 to 2001. *Allergy*. 2006;61:556-562.
4. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007;62:758-766.
5. Wieringa MH, Vermeire PA, Brunekreef B, Weyler JJ. Increased occurrence of asthma and allergy: critical appraisal of studies using allergic sensitization, bronchial hyper-responsiveness and lung function measurements. *Clin Exp Allergy*. 2001;31:1553-1563.
6. Braun-Fahrlander C, Gassner M, Grize L, et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur Respir J*. 2004;23:407-413.
7. Thomsen SF, Ulrik CS, Porsbjerg C, Backer V. Skin test reactivity among Danish children measured 15 years apart. *J Asthma*. 2006;43:151-153.
8. Toelle BG, Ng K, Belousova E, Salome CM, Peat JK, Marks GB. Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross sectional surveys over 20 years. *BMJ*. 2004;328:386-387.
9. Rönmark E, Bjerg A, Perzanowski M, Platts-Mills T, Lundback B. Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. *J Allergy Clin Immunol*. 2009;124:357-363.
10. Venter C, Hasan AS, Grundy J, et al. Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy*. 2010;65:103-108.
11. McGowan EC, Peng RD, Salo PM, Zeldin DC, Keet CA. Changes in food-specific IgE over time in the National Health and Nutrition Examination Survey (NHANES). *J Allergy Clin Immunol Pract*. 2016;4:713-720. pii: S2213-2198(16)30011-3.
12. Ben Shoshan M, Kagan RS, Alizadehfar R, et al. Is the prevalence of peanut allergy increasing? A 5-year follow-up study in children in Montreal. *J Allergy Clin Immunol*. 2009;123:783-788.
13. Baatenburg de Jong A, Dikkeschei LD, Brand PL. Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, monosensitized, and polysensitized children. *Pediatr Allergy Immunol*. 2011;22:166-171.
14. Baatenburg de Jong A, Dikkeschei LD, Brand PL. High prevalence of sensitization to aeroallergens in children 4 yrs of age or younger with symptoms of allergic disease. *Pediatr Allergy Immunol*. 2009;20:735-740.
15. Burr ML, Butland BK, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. *Arch Dis Child*. 1989;64:1452-1456.
16. Butland BK, Strachan DP, Lewis S, Bynner J, Butler N, Britton J. Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. *BMJ*. 1997;315:717-721.
17. von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy*. 1998;28:45-51.
18. Braback L, Hjern A, Rasmussen F. Trends in asthma, allergic rhinitis and eczema among Swedish conscripts from farming and non-farming environments. A nationwide study over three decades. *Clin Exp Allergy*. 2004;34:38-43.
19. Zollner IK, Weiland SK, Piechotowski I, et al. No increase in the prevalence of asthma, allergies, and atopic sensitization among children in Germany: 1992-2001. *Thorax*. 2005;60:545-548.
20. Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax*. 2007;62:91-96.
21. Linneberg A, Gislum M, Johansen N, Husemoen LLN, Jorgensen T. Temporal trends of aeroallergen sensitization over twenty-five years. *Clin Exp Allergy*. 2007;37:1137-1142.
22. Macan J, Varnai VM, Maloca I, Kanceljak-Macan B. Increasing trend in atopy markers prevalence in a Croatian adult population between 1985 and 1999. *Clin Exp Allergy*. 2007;37:1756-1763.
23. Laatikainen T, von Hertzen L, Koskinen JP, et al. Allergy gap between Finnish and Russian Karelia on increase. *Allergy*. 2011;66:886-892.
24. Platts-Mills TAE. The allergy epidemics: 1870-2010. *J Allergy Clin Immunol*. 2015;136:3-13.
25. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clin Exp Immunol*. 2010;160:1-9.
26. Wegienka G, Zoratti E, Johnson CC. The role of the early-life environment in the development of allergic disease. *Immunol Allergy Clin North Am*. 2015;35:1-17.
27. Azad MB, Konya T, Guttman DS, et al. Infant gut microbiota and food sensitization: associations in the first year of life. *Clin Exp Allergy*. 2015;45:632-643.
28. Abrahamson TR, Wu RY, Jenmalm MC. Gut microbiota and allergy: the importance of the pregnancy period. *Pediatr Res*. 2015;77:214-219.

29. Eigenmann PA, Atanaskovic-Markovic M, O'B Hourihane J, et al. Testing children for allergies: why, how, who and when: an updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation. *Pediatr Allergy Immunol*. 2013;24:195-209.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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